REMARKS

REGARDING APPLICATION STATUS

Claims 1-129 were pending. Claims 1-7 and 37-44 were rejected. Claims 8-36 and 45-129 were withdrawn from consideration. Non-elected claims 45-129 are cancelled herein to place the present application in a condition for allowance [MPEP 821.02].

Dependent claims 8-36 are to be rejoined with linking claims, upon finding an allowable linking base claim. Claims 1-6 and 37-39 are amended herein to more particularly point out and specifically claim subject matter of which the inventors consider as the invention. Support for the amendments presented herein can be found in the specification as originally submitted, particularly on page 2, lines 24-25, page 6, lines 8-10, page 15, lines 20-26, pages 16-18, page 25, lines 20-26, and page 26, lines 4-13. No new matter is introduced. By this Amendment, claims 1-44 are pending.

Special care has been taken in amending these claims to make the implicit explicit without raising new issues or changing the scope or direction of the claims. In particular, amended claims 1 and 2 now respectively recite the formerly implicit structural characteristics of the proteorhodopsin protein. That is, like rhodopsin, the proteorhodopsin protein has a secondary structure of seven transmembrane α-helices that form a pocket in which retinal is covalently linked [Spec. page 17, lines 18-25; Figure 5].

Moreover, claims 1 and 2 respectively recite a proteorhodopsin gene encoding a proteorhodopsin protein having the aforementioned structural characteristics. Unlike rhodopsins, these proteorhodopsin genes are isolated from naturally occurring bacteria [Spec. page 15, lines 20-25]. This is the essential link generic to all pending claims 1-44.

The specification and Figure 40 were objected. The specification is amended on page 2 to correct a misspelled word and on page 4 to make the implicit explicit. No new matter is introduced. More specifically, on page 2, line 19, "Archeal" should be "Archaeal" and on page 4, lines 11-12, "rhodopsin-like" refers to the "proteorhodopsin" in the next sentence that

starts with "More specifically". The objections and rejections are addressed hereinafter with general reference to the headings in the Office action.

REGARDING THE DEPOSIT OF BIOLOGICAL MATERIAL

The specification was objected to for lacking complete deposit information for the deposit of cells containing the clone BAC31A8. Although the examiner acknowledged that the specification discloses a deposit of the clones BAC31A8, BAC40E8, BAC41B4, BAC64A5 in ATCC on February 21, 2001, the examiner contended that it is not clear whether maintenance and availability requirements have been met. The examiner therefore required a filing of evidence of the reproducible production of these clones or cells containing these clones or filing of a deposit commensurate in scope with the claims.

The American Type Culture Collection (ATCC) is a well known International Depository Authority (IDA), *see,* <<http://www.atcc.org/Services/PatentDep.cfm>>. The examiner's attention is directed to MPEP 2405, which explains 37 C.F.R. 1.803, the controlling Rule that governs the recognition of acceptable depositories for patent purposes, and which lists IDAs, including ATCC, recognized under the Budapest Treaty. Accordingly, it is clear and one skilled in the art would have had no problem to recognize that the deposit dated February 21, 2001 met the maintenance and availability requirements under the Budapest Treaty.

Applicants nevertheless respectfully submit as evidence two official ATCC receipts (hereinafter referred to as Exhibit A). According to Exhibit A, "[t]he strains will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a U.S. Patent is issued citing the strains, and ATCC is instructed by the United States Patent & Trademark Office or the depositor to release said strains." In addition, "[t]he strains will be maintained for a period of at least 30 years from date of deposit, or five years after the most recent request for a sample, whichever is longer." Exhibit A was signed by Tanya Nunnally, a person having authority to represent ATCC and in a position to make such assurances. It is clear that the ATCC deposits met the maintenance and availability requirements under the Budapest Treaty. Therefore, the objection to the deposit of biological material is not applicable and should be withdrawn.

REGARDING THE DRAWINGS

Figure 40 was objected to for failing to show features as described in the specification. More specifically, Figure 40 as originally submitted is a black and white picture of two microfuge tubes, one of which contains a cell suspension with a reddish pigmentation, as described on page 26, lines 25-26, and page 27, lines 1-3. The examiner has required a proposed drawing correction or corrected drawings. To obviate this objection, Applicants hereby respectfully submit a corrected Figure 40 that shows, in color, a tube 4010 containing a cell suspension with a reddish pigmentation, as described in the specification [*id.*]. The corrected Figure 40 is a facsimile reproduction of the original color photo, on which the black and white Figure 40 is based. No new matter is introduced.

REGARDING THE CLAIM REJECTIONS UNDER 35 USC § 112, FIRST PARAGRAPH

Claims 1-6 and 37-44 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse the rejections for at least the reason that the examiner has made a giant leap beyond reasonable in interpreting the claimed "proteorhodopsin" as referring to "any rhodopsin".

There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) ("we are of the opinion that the PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims").

It is respectfully submitted that the examiner has not met the initial burden of presenting evidence or reasons why persons skilled in the art would <u>not</u> recognize in the disclosure a description of the invention defined by the claims. <u>On the contrary</u>, one skilled in the art would have readily recognized, upon reading and understanding the entire application disclosure including the specification, sequence listings, drawings, and claims, that the

invention is directed to a new type of *bacterial rhodopsin* retrieved from naturally occurring members of the domain Bacteria [*see, e.g.,* Spec. page 4, lines 5-15]. It is a misnomer to use *"bacterial rhodopsin"* to refer to the bacteriorhodopsin of the "*archaeal rhodopsin*" family of the Archaea or Archaebacteria kingdom. **Prior to the present invention, there is no true *"bacterial rhodopsin."*** The entire application disclosure describes this newly found true bacterial rhodopsin as "rhodopsin-like" and "proteorhodopsin," interchangeably. For example, in the specification, under the bold heading, "Proteorhodopsin," on page 15, line 19, proteorhodopsin gene and protein are defined as "rhodopsin-like gene and protein sequences retrieved from naturally occurring members of the domain Bacteria."

> Applicant may be his or her own lexicographer as long as the meaning assigned to the term is not repugnant to the term's well known usage. *In re Hill,* 161 F.2d 367, 73 USPQ 482 (CCPA 1947). Any special meaning assigned to a term "must be sufficiently clear in the specification that any departure from common usage would be so understood by a person of experience in the field of the invention." *Multiform Desiccants Inc. v. Medzam Ltd.,* 133 F.3d 1473, 1477, 45 USPQ2d 1429, 1432 (Fed. Cir. 1998).

The specification discloses, with sufficient clarity, that "proteorhodopsin" refers to "rhodopsin-like sequences from naturally occurring members of the domain Bacteria" [*see, e.g.,* Spec. page 4, lines 11-15]. The proteorhodopsin is "rhodopsin-like" because its topology is homologous to the rhodopsin protein family [Spec. page 17, lines 18-24]. However, the proteorhodopsin is not just any rhodopsin because the proteorhodopsin is derived from naturally occurring members of the domain Bacteria [Spec. page 15, lines 19-26]. Clearly, the specification teaches and claims "proteorhodopsin." One skilled in the art would have readily recognized that the specification neither teaches nor claims "a genus of nucleic acids which are different from those disclosed in the specification," as the examiner has alleged.

On the other hand, one skilled in the art would have agreed that "any rhodopsins" refers to rhodopsins from either the family of visual rhodopsins or the family of archaeal rhodopsins [Spec. page 2, lines 17-22]. The rejections, particularly those listed on page 5 of the Office action, would have been reasonable if the claimed invention indeed were directed to "any rhodopsin." Perhaps a brief overview of the invention, derived from the specification as originally filed and supported by scientific theories and facts well known in the art at the time

of the present application, would facilitate the examiner's understanding of the claimed invention.

Overview

A Long Felt Need in the Art – Economical Light-Driven Proton Pumps

Rhodopsin is the covalent complex of a large protein, *opsin*, and a small light-absorbing chromophore, *retinal*. It is well known in the art that rhodopsins are characterized by a secondary structure of seven transmembrane α-helices that form a pocket in which retinal is covalently linked [Spec. page 2, lines 16-25, *see, also,* J.A. Bieszke *et. al., Proceedings of National Academy of Sciences USA* 96:8034, 1999].

As discussed in the Background Art section of the specification, rhodopsins are known to belong to two distinct protein families, **visual rhodopsins** and **archaeal rhodopsins**, in two distinct kingdoms, Animal and Archaea, respectively. The former can be found in the eye throughout the animal kingdom and the latter could only exist in extreme halophilic environments, function as light-driven proton pumps (bacteriorhodopsins), chloride ion pumps (halorhodopsins), or photosensory receptors (sensory rhodopsins).

Bacteriorhodopsins are archaeal rhodopsins capable of generating a chemiosmotic membrane potential in response to light [Spec. page 3, lines 13-23]. The biochemical energy generated thereby has useful and practical applications in various fields such as bio-electronic and bio-material [*id.*]. Unfortunately, bacteriorhodopsins that originate from the Archaea can only adapt to extreme saline environments such as the Dead Sea or salt flats [*id.* at lines 23-25]. Since the isolation and cultivation of archaeal rhodopsins such as halorhodopsins is an elaborate process, one does not foresee a possible economic utilization thereof [Spec. page 4, lines 1-2, citing U.S. Pat. No. 5,290,699, considered by the examiner].

Bacterial Based Bacteriorhodopsins Solve The Aforementioned Long Felt Need in the Art

Taxonomically, archaeal rhodopsins belong to the Archaea (a.k.a. Archaebacteria) and not the Bacteria (a.k.a. Eubacteria or true bacteria) kingdom. Archaeal and bacterial cell walls have different chemical compositions. Archaebacteria have complex RNA polymerase

whereas bacteria have simple RNA polymerase. Simply put, archaebacteria are chemically distinct from bacteria. More importantly, all archaebacteria are extremophiles, which means that they all require extreme environments to live.

On the contrary, bacteria can be found and readily obtained from virtually everywhere. As discussed on page 5, lines 18-22, the proteorhodopsins of the present invention do not require extreme living environments and could be functionally expressed in *E. coli* or other bacterium. What is more, the proteorhodopsins of the present invention can be efficiently and economically produced in mass. This is an exciting advantage over known rhodopsins and particularly solves the long felt need in the art for economical light-driven proton pumps.

Proteorhodopsin Genes Isolated from Bacteria Encode Proteorhodopsin Proteins

The aforementioned J.A. Bieszke *et al.*'s articles, considered by the examiner, concur that **no** rhodopsin-like sequences have been reported in members of the domain Bacteria [Spec. page 3, lines 9-10]. The proteorhodopsins, as taught in the present application, are rhodopsin-like sequences derived from naturally occurring bacteria. The proteorhodopsins are "rhodopsin-like" because they are neither visual rhodopsins from the Animal kingdom nor archaeal rhodopsins from the Archaea kingdom.

The term, "proteorhodopsin," is first coined by the inventors of the present application in the provisional patent application No. 60/201,602, filed on May 3, 2000, the entire content of which has been incorporated by reference on page 1, lines 12-13, of the present application. The inventors subsequently published essentially the same content in "Bacterial Rhodopsin: Evidence for a New Type of Phototrophy in the Sea" *Science*, Vol. 289, September 2000, pp. 1902-1906, a copy of which is submitted herewith for the examiner's consideration.

In the specification, "proteorhodopsin" is identified and described in detail from page 15, starting from the bold heading of the same on line 19, to page 18, line 18. For example, the proteorhodopsin-containing contig (Sequence ID No:1), the open reading frame thereof encoding a proteorhodopsin [Page 16, lines 12-13], the nucleotide sequence of the proteorhodopsin gene (Sequence ID No:4), an exemplary secondary structure of

proteorhodopsin [FIG. 5], and a sequence listing of the native proteorhodopsin gene (Sequence ID No:6). Sequence ID No:1 specifically identifies, at lines <222> and <223>, a proteorhodopsin gene sequence (50866)..(51615).

The specification also discloses that the proteorhodopsin-containing contig was deposited on October 23rd, 2000 in GenBank under accession #AF279106, a copy of which is attached herewith. The specification as originally filed is consistent with the description on page 13 of the AF279106 document which indicates, under complement (50866..51615), product proteorhodopsin "has the properties of a light-driven proton pump when expressed with retinal in Escherichia coli."

The 35 U.S.C. § 112, First Paragraph, Rejections Were Not Based on "Proteorhodopsin"
Clearly, at the time of the invention, the applicants had possession of at least 30 representative sequences of proteorhodopsin genes. One skilled in the art would have had no problem recognizing that the applicants were in possession of the necessary common attributes or features of the elements possessed by these 30 representative proteorhodopsin sequences.

More specifically, the present application discloses that these new proteorhodopsin sequences share common features and attributes. At the minimum, all of the representative proteorhodopsin sequences are isolated from genomic fragments of members of naturally occurring bacteria. Further, although these representative proteorhodopsin sequences are derived from the domain Bacteria and not from the domain Archaea, they encode proteorhodopsin proteins having seven transmembrane domains, a typical feature of the rhodopsin protein family, that aligned well with the corresponding helices of the archaeal rhodopsins. This is specifically discussed in the specification on pages 17-18 with reference to Figure 5, which clearly shows that the secondary structure of the proteorhodopsin has seven transmembrane domains with amino acid residues forming a retinal binding pocket.

Variants of proteorhodopsin are similarly taught in pages 18-22, under the heading "Variants of Proteorhodopsin." These proteorhodopsin variants share the proteorhodopsin topologies,

though they may differ by as much as 31 nucleotides [Spec. page 20, lines 1-8]. Sequencing techniques are well known in the art. One skilled in the art could have readily deduced the upstream and downstream regions necessary to obtain a proteorhodopsin variant without undue experimentation [Spec. page 16, lines 6-19]. The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). Furthermore, as discussed above, the specification provides guidance in identifying, sequencing, and amplifying proteorhodopsin genes, *inter alia*, on pages 15-18.

The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997), cited by the examiner on page 6 of the Office action, does not apply here because "proteorhodopsin" is neither defined by function nor merely names a type of material which is generally known to likely exist. Again, as discussed above and in the specification, it is inherent that proteorhodopsin is structurally similar to rhodopsin. Prior to the invention, however, rhodopsin-like sequences have not been found to possibly exist outside visual rhodopsins and archaeal rhodopsins, with the exception of the "new eukaryotic opsin 1" (NOP-1) reported by J.A. Bieszke *et al., supra.*

Fiers v. Sugano as well as *Vas-Cath In. v. Mahurkar* (citation omitted), cited by the examiner on page 6 of the Office action, do not apply here inasmuch the claimed proteorhodopsin genes had been isolated, identified, deposited with the GenBank, and particularly described in the specification, as discussed above. Again, the specification specifically describes proteorhodopsin and particularly claims proteorhodopsin. To interpret "proteorhodopsin" as "any rhodopsin" is not only taxonomically incorrect but also an unreasonable stretch.

Claim 7 was rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The rejection is respectfully traversed.

Perhaps the examiner has not understood the second paragraph on page 16 of the specification, which discloses that the nucleotide sequence of the BAC clone BAC31A8 (Sequence ID No:1) has been deposited in GenBank under accession #AF279106 on October 23rd, 2000. In other words, the BAC clone BAC31A8 has been known and made publicly available since late 2000. A cursory GenBank search would have confirmed the deposit as well as its availability. Again, upon reading and understanding the entire application disclosure, as mentioned in the specification, page 16, lines 1-4, those of ordinary skill in the art would have had no problem in obtaining suitable DNA samples of naturally occurring bacteria from sources other than the Bacterial Artificial Chromosome (BAC) library. Furthermore, as discussed above, viable strains including the clone BAC31A8 had been deposited on February 21, 2001, with ATCC, a well-known IDA acceptable under 37 CFR 1.803, according to MPEP 2405. What is more, according to the cited Monaco *et al.* paper and the examiner's own statement on page 9, *para.* 13, of the Office action, BACs are well known in the art and BAC clones are stable over many generations.

"[I]t is incumbent upon the Patent Office, whenever a rejection on this [enablement] basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971).

REGARDING CLAIM INTERPRETATION

A) As discussed above, upon reading and understanding the entire application disclosure, one skilled in the art would have understood that, like rhodopsins, proteorhodopsin proteins are characterized by seven transmembrane α-helices that form a pocket in which retinal is covalently linked. Unlike rhodopsins, however, the proteorhodopsin genes encoding the proteorhodopsin proteins are derived from naturally occurring bacteria. Thus, proteorhodopsins are "rhodopsins-like" but do not belong to any known rhodopsins. The specification specifically describes proteorhodopsin and particularly claims proteorhodopsin. In view of the entire application disclosure, one of ordinary skill in the art would agree that

the claim interpretation was overly broad, since "any rhodopsin" would include subject matter beyond "proteorhodopsin," e.g., visual rhodopsin, archaeal rhodopsin, etc.

The inquiry into whether the description requirement is met must be determined on a case-by-case basis and is a question of fact. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. See, e.g., *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). The examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. The examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *Wertheim*, 541 F.2d at 263, 191 USPQ at 97. The misinterpretation of an essential claimed element is evidence that the examiner did not have a reasonable basis to challenge the adequacy of the written description. The rejections under 35 U.S.C. § 112, first paragraph, do not apply and should be withdrawn.

B) In claim 39, the phrase "for producing said proteorhodopsin protein in a host" was treated as an intended use of the product, and therefore was not taken into account when comparing the claim with prior art. Amended claim 39 no longer recites the phrase at issue.

REGARDING 35 USC § 102(b) REJECTIONS

Claims 1, 2, 5 and 37 were rejected under 35 U.S.C. § 102(b) as being anticipated by Kitajima *et al.* (Biiochem. Biophys. Res. Comm., vol. 220, pp. 341-345, 1996, hereinafter referred to as the "Kitajima paper"). The rejections are respectfully traversed.

The Kitajima paper is taxonomically incorrect. *Haloarcula vallismortis* is not a member of the domain Bacteria and hence **not** a bacterium. The organism classification is as follows: Archaea; Euryarchaeota; Halobacteria; Halobacteriales; Halobacteriaceae; Haloarcula [source: NCBI Taxonomy database, Taxonomy ID: 28442, <http://ncbi.nlm.nih.gov/>]. It has long been known that *Haloarcula* and like species belong to the Archaea and that halophilicc archaea cannot grow in the marine environments.

The cited paragraph on page 341 refers to the National Collection of Marine Bacteria, Ltd., Aberdeen (NCMB), from where *Haloarcula vallismortis* can be purchased. It is known in the art that 'bacterial' culture collections typically stock both archaea and bacteria from a variety of sources. *Haloarcula vallismortis* is **not** marine – it was isolated in salt pools in Death Valley, California. The medium described in reference [10] of the Kitajima paper refers to a high NaCl medium (20% NaCl) typically required for extremely halophilic archaea, nearly 10 times the salt concentration in the ocean and typical marine media. Extremely halophilic archaea require 5-10 times the salinity of seawater to grow, and contain correspondingly high internal salt concentrations. This is consistent with the physiology of *Haloarcula vallismortis*, its rRNA phylogeny, and the relationship of its rhodopsins to those of other extremely halophilic rhodopsins. In short, the Kitajima paper does not disclose or anticipate a proteorhodopsin gene isolated from a genomic fragment of a naturally occurring marine bacterium. The rejections are therefore not applicable and should be withdrawn.

REGARDING 35 USC § 103(a) REJECTIONS

Claim 6 was rejected under 35 U.S.C. § 103(a) as being unpatentable over the Kitajima paper in view of Monaco *et al.* (Trends in Biotech., vol. 12, pp. 280-286, 1994). The rejection is respectfully traversed.

It would not have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have "used BACs of Monaco *et al.* to clone bacterial fragments of Kitajima *et al.*," as the examiner has alleged, because not only *Haloarcula vallismortis* is not a marine bacterium, it is not a bacterium at all. Since *Haloarcula vallismortis* can only live in extremely salty environments, it would not be possible, and there is no good reason, to use BACs to clone archaeal fragments. What is more, Figure 1 of the present application clearly shows that Halobacterium salinarum is unrelated to the claimed *bacterial* proteorhodopsin.

For similar reasons, the alleged various combinations of the Kitajima paper in view of Shimono *et al.* (FEBS Letters, vol. 420, pp. 54-56, 1997), Zozulya *et al.* (Protein Eng., vol. 3, pp. 453-458, 1990), and Mollaaghababa *et al.* (PNAS, vol. 93, pp. 11482-11486, 1996)

would have suffered the same fatal weakness and thus are not viable combinations under 35 U.S.C. 103(a). Accordingly, a *prima facie* case of obviousness has not been established.

Conclusion

The present application sufficiently describes and accurately claims proteorhodopsin genes encoding proteorhodopsin proteins. In view of the entire application disclosure and considering what was known at the time of the invention, one skilled in the art would have had no problem to recognize that the inventors had isolated, identified, deposited, possessed, described, and claimed new, distinct, viable, and useful proteorhodopsin genes encoding proteorhodopsin proteins. None of the cited prior art teaches, anticipates, or even suggests the possibility of isolating rhodopsin-like sequences from bacteria.

The new proteorhodopsin genus as taught and claimed in the present invention is important to the society as a whole. A cursory search on the Internet would confirm that many ongoing proteorhodopsin research are being conducted *after* the inventors published their findings. Perhaps E. Pennisi's statement in "High-Tech Lures Hook Into New Marine Microbes" Science, vol. 289, p. 1869, 15 September 2000, explains why proteorhodopsin was an entirely unexpected phenomenon:

> "Few microbiologists have imagined that aerobic phototrophic bacteria could live on the ocean's surface, because they usually thrive where the water's oxygen content is low. And even fewer suspected that some bacteria might have a bacteriorhodopsin."

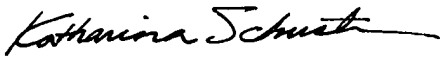
For the foregoing reasons, it is respectfully submitted that the present invention is patentably distinct from, not anticipated by, and unobvious over the Kitajima paper in view of a collection of secondary references discussed above. It is further respectfully submitted that the linking claims 1 and 2 respectively recite subject matter not reached by the closest prior art of record under 35 USC §§ 102(b) and/or 103(a) and therefore should be allowed.

Reliance is placed on *In re* Fine, 5 USPQ 2d 1596, 1600 (Fed. Cir. 1988) and *Ex parte* Kochan, 131 USPQ 204 (Bd. App. 1960) for allowance of the dependent claims 3-44, since

they differ in scope from their parent independent claim 2, which is submitted to be patentable. It is respectfully requested that dependent claims 8-36 be rejoined.

This Reply is submitted to be complete and proper in that it places the present application in a condition for allowance without adding new matters. Since the examiner has done a thorough search in the first Office action in light of the entire application disclosure and claims, no new search should be necessary. Favorable consideration and a Notice of Allowance of all pending claims are therefore earnestly solicited. The examiner is sincerely invited to telephone the undersigned for discussing an examiner's Amendment or any suggested actions for accelerating prosecution and moving the present application to allowance.

Respectfully submitted,



Katharina Wang Schuster, Reg. No. 50,000

Ron Jacobs, Ph.D., Reg. No. 50,142

Patent Attorney/Agent for the Applicants

LUMEN INTELLECTUAL PROPERTY SERVICES
2345 Yale Street, Second Floor
Palo Alto, CA 94306
(O) 650-424-0100 (F) 650-424-0141

(Attachment: Exhibit A)